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ORIGINAL ARTICLE

# Concomitant Rotavirus and *Salmonella* Infections in Children with Acute Diarrhea

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## KEY WORDS:

acute gastroenteritis;  
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**Background and purpose:** The incidence of concomitant rotavirus and *Salmonella* infection has been reported to be 1.3% to 7.4%. We designed this study to compare the clinical manifestations in children infected with rotavirus, *Salmonella*, or both.

**Methods:** The medical records of admitted children with acute rotavirus or *Salmonella* gastroenteritis in 2001 were reviewed. They were divided into group R (rotavirus), group S (*Salmonella*) and group C (concomitant infection with both). The differences of clinical manifestations and laboratory data among the three groups were analyzed via chi-squared, analysis of variance (ANOVA), Bonferroni and Kruskal-Wallis tests, and odds ratios with 95% confidence intervals (95% CI).

**Results:** Among the 895 cases reviewed, 550 were group R, 312 group S, and 33 (3.7%) group C. Group C had more vomiting compared with group S ( $p=0.0017$ ). Comparing with group R, group C had more prolonged and high fever ( $\geq 39^\circ\text{C}$ ) ( $p<0.05$ ), more percentage of green coloration, with mucus and blood contained in the stool ( $p<0.001$ ). The C-reactive protein (CRP) value was significantly higher in group C ( $9.70 \pm 11.05$  mg/dL) than in group R ( $1.33 \pm 3.62$  mg/dL) or S ( $5.22 \pm 6.11$  mg/dL) ( $p<0.05$ ). Hypokalemia was found most frequently in group C (C: 30.0%, S: 8.8%, R: 7.3%) ( $p=0.0026$ ).

**Conclusion:** Concomitant rotavirus and *Salmonella* infections accounted for 3.7% of cases in this study. Patients in group C (30.0%) had a significantly higher incidence of hypokalemia than group R (7.3%) or S (8.8%). Group C consisted of 33 cases of the 895 reviewed cases (3.7%). In a child with rotavirus gastroenteritis, concomitant infection with *Salmonella* should be considered if the child has sustained a high fever ( $\geq 39^\circ\text{C}$ ) for over 4 days and a green stool with mucus and blood.

## 1. Introduction

Rotavirus is the most common viral and *Salmonella* the most common bacterial cause in children with acute diarrhea.<sup>1–3</sup> Their similar findings were delineated in previous reports in Taiwan.<sup>4–9</sup> The clinical features of infection with only one agent are fairly

distinctive. Rotavirus gastroenteritis tends to cause mild to moderate fever, vomiting, and a watery stool. Most fatalities occur in infants with poor access to medical care and are attributed to dehydration.<sup>2</sup> The epidemiology of rotavirus infection is heavily influenced by the local climate. Although rotavirus has been identified as the major pathogen associated

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with “winter” gastroenteritis, the seasonal peak may vary with different climates.<sup>6</sup> *Salmonella* infection occurs with its highest frequency in the warm months.<sup>10</sup> *Salmonella* infection is more likely to present with fever, crampy abdominal pain, and blood mixed with the stool.<sup>11</sup> The incidence of concomitant rotavirus and *Salmonella* infection has been reported to be 1.3% to 7.4%.<sup>12,13</sup> However, the clinical manifestations in children hospitalized with simultaneous rotavirus and *Salmonella* infections have not been well described. We designed this study to compare the clinical findings in children infected with rotavirus, *Salmonella*, or both.

## 2. Materials and Methods

The medical records of 1114 children admitted to Mackay Memorial Hospital with acute rotavirus or *Salmonella* gastroenteritis from January to December 2001 were reviewed. Patients complicated with intestinal perforation were excluded. We also excluded patients who had underlying diseases such as neuroblastoma, myopathy, histiocytosis, acute pyelonephritis, etc., leaving 895 records for review. The stool samples had been studied for bacterial culture and rotavirus antigen simultaneously at admission. Stool and blood cultures were performed by using selective media plates, including a *Salmonella*–*Shigella* medium and a Hektoen enteric medium. *Salmonella* serogrouping was determined by using commercial antiserum (Denka Seiken Co.). An enzyme immunoassay (Premier Rotaclone) was used to detect the rotavirus antigen in fecal specimens. They were divided into group R (rotavirus), group S (*Salmonella*) and group C (concomitant infection with both pathogens). Clinical manifestations and laboratory data were recorded to compare the differences among the three groups. A chi-square test was used to detect the difference of categorical variables; whereas analysis of variance (ANOVA) was used to detect the difference of continuous variables. When the ANOVA test gave a significant difference, then Bonferroni test was used as a posteriori-hoc test. The Kruskal-Wallis test was used for detecting the mean difference on C-reactive protein (CRP) in pathogens since the normal distribution was not assumed. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. A *p* value of less than 0.05 was defined as significant.

## 3. Results

Among the 895 cases of acute diarrhea reviewed, 550 (61.4%) were caused by rotavirus alone (group R), 312 (34.9%) by *Salmonella* alone (group S), and 33 (3.7%) by both pathogens (group C). There were

499 males and 396 females in the study sample, with the ratio of male to female in each group as follows: group C, 18:15; group R, 309:241; and group S, 172:140. The gender ratios did not differ significantly among the three groups (*p*=0.946) (Table 1). The mean ( $\pm$ SD) age in months at admission for group C was 21.2 $\pm$ 23.7; for group R, 23.7 $\pm$ 18.2 and for group S, 19.5 $\pm$ 21.6. The interval between date of onset and date of admission in group C was 2.6 $\pm$ 1.9 days in group R, 2.4 $\pm$ 2.0 days and in group S, 3.2 $\pm$ 2.5 days. There was no significant difference in the interval between group C and the other two groups. The length of hospital stay in groups C (7.1 $\pm$ 3.7 days) and S (6.6 $\pm$ 3.5 days) were significantly greater than that of group R (4.6 $\pm$ 1.9 days; *p*<0.05), but there was no difference between groups C and S (Table 1). The peak of seasonal occurrence in group C (September, 27.3%) was between those of group R (May, 12.4%, and October, 12.1%) and group S (June, 15.4%, July, 13.5%, and August, 16.4%) (Table 1).

The percentages of patients with high fever (i.e. a temperature  $\geq$ 39°C) in groups C (85.2%, OR [95% CI]3.3[1.1–9.7], *p*=0.0222) and S (83.1%, OR [95% CI]2.8[1.9–4.2], *p*<0.001) were significantly greater than in group R (63.5%), with no significant difference between groups C and S (*p*=0.7846) (Table 1). The duration of fever in group C was significantly longer than that in group R (C: 4.8 $\pm$ 2.7 days, R: 3.0 $\pm$ 1.8 days; *p*<0.05). Significantly more children in group C had vomiting compared with group S (C: 66.7%, OR [95% CI]0.6[0.3–1.2], S: 38.5%, OR [95% CI]0.2[0.1–0.2]; *p*=0.0017). The mean daily frequency of diarrhea in group S was significantly more than that in group R (S: 7.6 $\pm$ 3.7, R: 6.5 $\pm$ 3.4; *p*<0.05), but there was no significant difference between group C and the other two groups. However, significantly more children in group C had green stools compared group R (C: 57.6%, OR [95% CI]4.3[2.1–8.8], R: 24.1%; *p*<0.001). There were significant differences in the presence of mucus (R: 18.9%, S: 54.2%, OR [95% CI]5.1[3.7–6.9], C: 33.3%, OR [95% CI]2.1[1.0–4.6]; *p*<0.001) and blood (R: 7.1%, S: 59.6%, OR [95% CI]16.1[10.8–24.0], C: 24.2%, OR [95% CI]3.5[1.5–8.3]; *p*<0.001) in the stool. The groups did not differ significantly in terms of abdominal bloating (R: 70.7%, S: 77.2%, OR [95% CI]1.4[1.0–1.9], C: 69.7%, OR [95% CI]1.0[0.4–2.0]; *p*=0.107), pain (R: 17.3%, S: 18.3%, OR [95% CI]1.1[0.7–1.5], C: 9.1%, OR [95% CI]0.5[0.1–1.6]; *p*=0.415), seizures (R: 3.8%, S: 2.2%, OR [95% CI]0.6[0.2–1.4], C: 3%, OR [95% CI]0.8[0.1–6.0]; *p*=0.454), or dehydration (R: 14.6%, S: 14.1%, OR [95% CI]1.0[0.6–1.4], C: 21.2%, OR [95% CI]1.6[0.7–3.8]; *p*=0.544). However, flu-like symptoms were significantly more common in group R compared with group S (R: 48.9%, S: 36.5%, OR [95% CI]0.6[0.5–0.8]; *p*=0.0004) (Table 1).

**Table 1** Symptoms of rotavirus, *Salmonella*, and concomitant infections

Clinic manifestation	Rotavirus infection	<i>Salmonella</i> infection	Concomitant infection	<i>p</i> value
Sex (male/female)	309/241	172/140	18/15	0.946
OR (95% CI)	1.0	1.0 (0.7–1.3)	0.9 (0.5–1.9)	
Age (mo)	23.7±18.2	19.5±21.6	21.2±23.7 <sup>†</sup>	0.010
( <i>n</i> , range)	(550, 0–135)	(312, 1–180)	(33, 1–185)	
Days from onset to admission ( <i>n</i> , range)	2.4±2.0 (545, 0–13)	3.2±2.5 (311, 0–18)	2.6±1.9 <sup>†</sup> (33, 0–9)	0.001
Length of stay (days)	4.6±1.9*	6.6±3.5	7.1±3.7	0.001
( <i>n</i> , range)	(550, 1–15)	(312, 1–20)	(33, 3–19)	
Days from onset to discharge ( <i>n</i> , range)	7.0±2.8* (546, 2–28)	9.8±4.5 (312, 2–35)	9.7±4.5 (33, 4–24)	0.001
Fever	499/550 (90.7%)	292/311 (93.9%)	32/33 (97.0%)	0.1459
OR (95% CI)	1.0	1.6 (0.9–2.7)	3.3 (0.4–24.4)	
BT ≥39°C	259/408 (63.5%)*	187/225 (83.1%)	23/27 (85.2%)	<0.001
OR (95% CI)	1.0	2.8 (1.9–4.2)	3.3 (1.1–9.7)	
Duration (days)	3.0±1.8*	5.3±2.7	4.8±2.7	<0.001
( <i>n</i> , range)	(458, 1–17)	(260, 1–18)	(30, 2–12)	
Flu	269/550 (48.9%)	114/312 (36.5%)	13/33 (39.4%) <sup>†</sup>	0.002
OR (95% CI)	1.0	0.6 (0.5–0.8)	0.7 (0.3–1.4)	
Vomiting	430/550 (78.2%)	120/312 (38.5%)*	22/33 (66.7%)	<0.001
OR (95% CI)	1.0	0.2 (0.1–0.2)	0.6 (0.3–1.2)	
Bloating	389/550 (70.7%)	241/312 (77.2%)	23/33 (69.7%)	0.107
OR (95% CI)	1.0	1.4 (1.0–1.9)	1.0 (0.4–2.0)	
Pain	95/550 (17.3%)	57/312 (18.3%)	3/33 (9.1%)	0.415
OR (95% CI)	1.0	1.1 (0.7–1.5)	0.5 (0.1–1.6)	
Dehydration	80/550 (14.6%)	44/312 (14.1%)	7/33 (21.2%)	0.544
OR (95% CI)	1.0	1.0 (0.6–1.4)	1.6 (0.7–3.8)	
Seizure	21/550 (3.8%)	7/312 (2.2%)	1/33 (3.0%)	0.454
OR (95% CI)	1.0	0.6 (0.2–1.4)	0.8 (0.1–6.0)	
Stool times (days)	6.5±3.4	7.6±3.7	7.0±2.4 <sup>†</sup>	<0.001
( <i>n</i> , range)	(430, 1–25)	(285, 1–30)	(25, 3–10)	
Stool color				
Yellow	417/549 (75.9%)	131/312 (42.0%)	14/33 (42.4%)	
OR (95% CI)	1.0	0.2 (0.2–0.3)	0.2 (0.1–0.5)	
Green	132/549 (24.1%)*	181/312 (58.0%)	19/33 (57.6%)	<0.001
OR (95% CI)	1.0	4.4 (3.2–5.9)	4.3 (2.1–8.8)	
Stool mucus <sup>‡</sup>	104/550 (18.9%)	169/312 (54.2%)	11/33 (33.3%)	<0.001
OR (95% CI)	1.0	5.1 (3.7–6.9)	2.1 (1.0–4.6)	
Stool blood <sup>‡</sup>	39/550 (7.1%)	186/312 (59.6%)	8/33 (24.2%)	<0.001
OR (95% CI)	1.0	16.1 (10.8–24.0)	3.5 (1.5–8.3)	

\*Significantly different from the other two groups ( $p < 0.05$ ). <sup>†</sup>Not significantly different from the other two groups ( $p > 0.05$ ).

<sup>‡</sup>Significant difference among all three groups ( $p < 0.05$ ). BT = Body temperature; OR = odds ratios; CI = confidence intervals.

The percentage of *Salmonella* serogroups in the stool cultures of patients in group C vs. group S were as follows: B, 56.0% vs. 48.5%; C, 16.9% vs. 24.3%; D, 24.1% vs. 21.2%; E, 0.7% vs. 3.0%; and untyped species, 2.3% vs. 3.0%. In group C cultures, 59.4% of isolates were resistant to ampicillin, compared with 40.3% in group S ( $p = 0.0379$ ). One isolate in group C and two in group S were resistant to ceftriaxone.

The percentages of children with bacteremia were 3.0% in group C and 11.2% in group S.

There was no significant intergroup difference in white blood cell (WBC) count (R: 10,797±4679/mm<sup>3</sup>, S: 10,734±4375/mm<sup>3</sup>, C: 11,330±3630/mm<sup>3</sup>;  $p = 0.774$ ) or in the incidence of hyponatremia (R: 12.5%, S: 11.2%, OR [95% CI] 0.9 [0.5–1.7], C: 5.0%, OR [95% CI] 0.4 [0.1–2.3];  $p = 0.5860$ ) (Table 2). However,

**Table 2** Laboratory data in rotavirus, *Salmonella*, and concomitant infections

	Rotavirus infection	<i>Salmonella</i> infection	Concomitant infection	<i>p</i> value
WBC (/mm <sup>3</sup> ) ( <i>n</i> , range)	10,797±4679 (549, 2580–35,500)	10,734±4375 (310, 1360–35,610)	11,330±3630 (33, 6200–20,360)	0.774
ESR (mm/hr) ( <i>n</i> , range)	18.0±13.0 (81, 2–75)	35.0±17.5* (38, 10–87)	16.8±9.3 (5, 7–29)	<0.001
CRP (mg/dL) <sup>†</sup> ( <i>n</i> , range)	1.33±3.62 (293, 0–14.8)	5.22±6.11 (214, 0–29.9)	9.70±11.05 (23, 0–31.1)	<0.001
CRP > 0.8 (mg/dL) OR (95% CI)	94/298 (31.5%)* 1.0	173/225 (76.9%) 7.2 (4.9–10.7)	14/23 (60.9%) 3.4 (1.4–8.1)	<0.001
CRP > 10 (mg/dL) <sup>†</sup> OR (95% CI)	6/293 (2.1%) 1.0	35/214 (16.4%) 9.4 (3.9–22.7)	9/23 (39.1%) 30.8 (9.6–98.5)	<0.001
Na < 135 (mEq/L) OR (95% CI)	36/288 (12.5%) 1.0	14/125 (11.2%) 0.9 (0.5–1.7)	1/20 (5.0%) 0.4 (0.1–2.3)	0.5860
K < 3.5 (mEq/L) OR (95% CI)	21/286 (7.3%) 1.0	11/125 (8.8%) 1.2 (0.6–2.6)	6/20 (30.0%)* 3.8 (1.4–10.4)	0.0026

\*Significantly different from the other two groups ( $p < 0.05$ ). <sup>†</sup>Significant difference among all three groups ( $p < 0.05$ ). WBC = white blood cell; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; OR = odds ratios; CI = confidence intervals; mEq/L = milliequivalents per litre.

patients in group C (30.0%, OR [95% CI] 3.8 [1.4–10.4]) had a significantly higher incidence of hypokalemia than group R (7.3%,  $p = 0.0006$ ) or S (8.8%, OR [95% CI] 1.2 [0.6–2.6],  $p = 0.0062$ ). The CRP value in group C (9.70±11.05 mg/dL) was significantly higher than in groups R (1.33±3.62 mg/dL,  $p < 0.05$ ) and S (5.22±6.11 mg/dL,  $p < 0.05$ ). Using a cutoff for CRP of >0.8 mg/dL, the percentage of patients with an elevated value was significantly greater in groups S (76.9%, OR [95% CI] 7.2 [4.9–10.7],  $p = 0.0041$ ) and C (60.9%, OR [95% CI] 3.4 [1.4–8.1],  $p < 0.0001$ ) than in group R (31.5%), but there was no difference between group C and S ( $p = 0.0893$ ). Using a cutoff of >10 mg/dL, significantly more children in group C (39.1%, OR [95% CI] 30.8 [9.6–98.5]) had an elevated value compared with groups R (2.1%,  $p < 0.0001$ ) and S (16.4%, OR [95% CI] 9.4 [3.9–22.7],  $p = 0.0076$ ). The mean ESR in group S (35.0±17.5 mm/hr) was significantly greater than in groups R (18.0±13.0 mm/hr,  $p < 0.05$ ) and C (16.8±9.3 mm/hr,  $p < 0.05$ ) (Table 2). However, only 5 of the 33 patients in group C had an ESR recorded in the record.

#### 4. Discussion

Rotavirus and *Salmonella* were found to be the most common pathogens in viral and bacterial diarrhea in children. The same results were reported in the previous data in Taiwan.<sup>14,15</sup> The differentiation between them is important because they may have different complications and need different treatment. However, concomitant rotavirus and *Salmonella* infection did occur (3.7% in this study). A previous

study identified vomiting as a key clinical feature that was significantly more common among patients with rotavirus than among those with diarrhea due to other causes.<sup>16</sup> In comparison of rotavirus or non-specified gastroenteritis with *Salmonella* enteritis, the latter was significantly more likely to lead to blood and mucus in the stool, fever during admission, more stools per day, a longer hospital stay, and to occur in younger patients.<sup>17</sup> In this study, we found that patients with concomitant rotavirus and *Salmonella* infections tended to be more seriously ill than those with rotavirus alone. They had not only vomiting, but also sustained fever ( $\geq 39^\circ\text{C}$ ) for more than 4 days, and a green stool with mucus and blood. It has been reported there was a close relationship between rotavirus and benign afebrile seizure.<sup>18–21</sup> In this study, seizures were rare (<4%), with no different incidence between the three groups.

The white blood cell (WBC) count is not helpful in diagnosing bacterial enteritis in children,<sup>22</sup> and our findings were consistent with this statement. Another group has suggested that a CRP > 1.2 mg/dL may be useful for predicting bacterial gastroenteritis in children.<sup>23</sup> Conversely, a high negative predictive value for a low CRP (<2.0 mg/dL) might allow clinicians to reliably exclude *Salmonella* as a cause of gastroenteritis.<sup>22</sup> Our study revealed that when using a low cutoff for CRP (>0.8 mg/dL) the percentage of patients with concomitant infection who had a positive result was between that for *Salmonella* or rotavirus infection alone. The percentage of patients with concomitant infection who had a CRP > 10 mg/dL was also significantly greater than in the other two groups. Overall, patients with concomitant



infection had higher CRP values than those with rotavirus infection alone. Hypokalemia was also most frequent in concomitant infection, but a reported predisposition to hyponatremia in *Salmonella* enteritis was not substantiated in our study.<sup>13</sup>

Chang reported that bacteremia occurred in 38% of *Salmonella*-infected patients less than 3 months of age.<sup>24</sup> *Salmonella* bacteremia also has been documented in afebrile, well-appearing children, especially neonates.<sup>10</sup> On the other hand, most newborns infected with rotavirus are afebrile.<sup>2</sup> In our study, only one third of children under 3 months of age had fever.

The most common pathogen in the *Salmonella* enteritis cases was serogroup B, which was also the most common pathogen in both concomitant infection and isolated *Salmonella* infection in this study.<sup>25–27</sup> We also found that the serogroup B *Salmonella* in concomitant infection had higher incidence of resistance to ampicillin. Although Bukholm's study indicated a specific interaction between rotavirus-infected cells and facultatively intracellular enteropathogenic bacteria, the mechanism of ampicillin resistance in the *Salmonella* strain involved in concomitant rotavirus and *Salmonella* infection is not clear.<sup>28</sup>

Our study indicated that the lengths of hospitalization for children with concomitant infection and those with *salmonella* alone were similar, and for both groups, length of hospitalization was significantly longer than that for the rotavirus group. This is consistent with the findings of a study in Singapore.<sup>3</sup>

In summary, concomitant rotavirus and *Salmonella* infection accounted for 3.7% of cases in this study. There may be an elevated CRP and hypokalemia. In a child with rotavirus gastroenteritis, concomitant infection with *Salmonella* should be considered if the child has a sustained high fever ( $\geq 39^{\circ}\text{C}$ ) for over 4 days and a green stool with mucus and blood.

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